ZEBRAS OF MEDICINE:
ATOPIC DERMATITIS AND HYPER IGE SYNDROME, WHEN TO SUSPECT PRIMARY IMMUNODEFICIENCY?

Aster Witvliet[1]

[1] Master's student Medical Biology, Radboud university, Nijmegen, The Netherlands

Abstract

Insight

Atopic dermatitis (AD) is the most frequent cause of eczema and is associated with allergies, increased risk for skin infections, and high blood serum IgE levels. Atopic dermatitis considerably overlaps with the clinical presentation of the Hyper IgE syndromes (HIES), a set of rare primary immunodeficiencies. Especially in young children, diagnosis of HIES can be difficult considering that many characteristic signs of HIES, other than eczema, only develop at a later stage. Early diagnosis is beneficial for managing HIES as it allows for early initiation of targeted treatment and early consideration for hematopoietic stem cell transplantation. Thus, differentiating AD and HIES in young children is of considerable importance. This article delineates the overlap and differences between AD and HIES, with a particular focus on the mechanisms behind predispositions to infections, that can help raise suspicion of HIES in patients presenting with AD-like eczema.

KEYWORDS: Eczema, recurrent infections, HSCT, STAT3, DOCK8

Dermatitis, also often referred to as eczema, is a very common condition that is most often caused by atopic dermatitis (AD) [1]. AD often first presents in childhood, and many patients outgrow it before adolescence [2]. In the Netherlands, the general population prevalence is 3%, but for children between the ages of 0 and 10, the prevalence ranges from 6-12% [3]. AD is a chronic inflammatory skin disease and is likely caused by a combination of skin barrier dysfunction, immune system dysfunction, and environmental factors [2]. AD is associated with, among others, itching that causes sleep interruptions, an increased risk of allergies, and an increased risk of infections [2]. While AD can be challenging to manage in some cases, the condition and its associated manifestations are generally non-life-threatening [4]. However, the chronic eczema that is present in AD can also be a symptom of a set of rare primary immunodeficiency disorders (PIDs): the Hyper-IgE syndromes (HIES) [1]. PIDs are inborn errors of the immune system, and, currently, more than 350 different disorders are recognised [5]. In the Netherlands, the five-year incidence of PID is 6.8 in 100,000 [6]. Early diagnosis of a PID is of the utmost importance for better management of the condition and, in some cases, allows for life-saving haematopoietic stem cell transplantation (HSCT) [7, 8]. While chronic eczema is a symptom of many PIDs, HIES and severe AD can be especially hard to distinguish due to overlap in clinical presentation [1, 9].

Currently, five types of HIES have been described, each with a different gene affected; *STAT3, DOCK8, PGM3, CARD11,* and *ZNF431* [7]. *STAT3* deficiency and *DOCK8* deficiency are the most well-characterised HIES; thus, this paper will primarily focus on these types of HIES [7, 9]. The HIES are generally characterised by a triad of AD-like eczema, elevated IgE levels, and recurrent infections [7]. Furthermore, other symptoms, such as skeletal and dental abnormalities, are associated with the condition, dependent on the type of HIES [7]. Nevertheless, while the triad symptoms are incredibly common in HIES patients, they are very unspecific and can especially be confused with severe AD [9, 10]. Therefore, the triad symptoms are unsuitable for the diagnosis of HIES [9]. The elevated IgE levels to which the HIES thank their name are also highly prevalent in AD [11]. Furthermore, AD patients have an increased risk of infections [12, 13]. However, the difference in type and severity of the infections that are to be expected in HIES versus those to be expected in AD can help distinguish these two diseases [9, 10]. The official diagnosis of HIES is based on the National Institutes of Health HIES scoring system that can successfully distinguish between HIES and AD in older children [10]. However, this scoring system is not always successful at diagnosing HIES in younger children, as many symptoms might only arise at a later age [9]. HIES patients often have a considerably large diagnostic delay; for example, in the Netherlands, diagnosis on average takes 10.5 years from the first presentation of symptoms [6]. Overall, a diagnostic delay is caused by a combination of the rarity of the condition, the often nonspecific symptoms that are easily confused with AD, and the specific symptoms only arising at a later age [9-11].

This review compares AD and HIES with a focus on their associated infections and underlying disease mechanisms to help determine a suspicion of HIES at a younger age, thereby improving early diagnosis. Additionally, differences in treatment between AD and HIES are discussed.

Disease mechanism

The key to distinguishing AD from HIES is through understanding the underlying mechanisms causing the infectious complications in these conditions. Patients with AD have an increased chance of skin infections, likely due to various risk factors associated with AD [13]. Currently, the exact cause of AD is incompletely understood but likely involves genetic factors, a dysfunctional immune response, and environmental factors [14-16]. In AD, the combination of these three factors can work together to impair many aspects of the defences of the skin barrier leading to an increased risk of skin infections [2]. The skin defends against infections through four main barriers: the physical barrier, the chemical barrier, the immunological barrier, and the microbiome barrier [14]. In AD, there are many mechanisms through which the skin barrier is thought to become impaired. A few of these mechanisms will be further outlined.

The physical barrier of the skin consists of the stratum corneum (the outermost layer of the skin) and the tight junctions between epithelial cells [14]. When the physical skin barrier becomes dysfunctional, for example due to genetic predisposition, the skin barrier will more easily be penetrated by an allergen or irritant [2]. The allergens or irritants, when processed by an antigen-presenting cell in the skin,

can trigger Th2 cells to produce type two inflammatory cytokines [2, 17]. This inflammatory response can, in turn, further damage the physical skin barrier, worsening skin barrier degradation, and, additionally, can cause an impaired chemical barrier [14]. An essential feature of the chemical barrier of the skin is secreted antimicrobial peptides, which help prevent infection [18]. The type two inflammatory response contains IL-4 and IL-13, which have been shown to cause a reduction of antimicrobial peptide production in the skin, leading to an increased risk of skin infection [19, 20]. Not only a defective skin barrier but likely also a change in the microbiome can lead to inflammation in the skin. Skin affected by AD is very susceptible to colonisation by *Staphylococcus aureus (S. aureus)*; a recent meta-analysis found that 70% of AD patients carried *S. aureus* [21]. Superantigens produced by *S. aureus* can enhance type two inflammation, causing a breakdown of the skin barrier and a reduction of antimicrobial peptide secretion, which, in turn, further increases the risk of infection [22].

Skin infections in AD are primarily bacterial infections with *S. aureus*, but other infections occur as well [21]. While *S. aureus* can be found on healthy skin, the combination of a dysfunctional skin barrier and high rates of *S. aureus* colonisation likely predispose AD patients to skin infections with *S. aureus* [23]. Furthermore, AD skin is more susceptible to viral infection with the herpes simplex virus type 1 (HSV-1), which causes eczema herpeticum (EH) and is experienced by 3% of patients [24]. Exposure to HSV-1 is common, but only a small subset of AD patients experience EH, indicating that other environmental or host factors are necessary for the development of EH [24]. Finally, AD patients also have an increased risk for fungal infections of the skin, likely caused by skin barrier defects, allowing usually harmless fungal species to colonise and cause infection [25].

Patients with HIES have a more generally increased risk of infections because genetic mutations cause a dysfunctional immune system [7]. HIES patients are highly susceptible to bacterial and fungal infections, which will often be recurrent and difficult to treat [9]. In both STAT3-HIES and DOCK8-HIES, a combination of deficiencies of Th17 cells and antibodies appear to be very important for this susceptibility [7]. Th17 cells are a type of T-helper cells that, through the secretion of IL-17 and IL-22, stimulate epithelial cells to secrete chemokines and antimicrobial peptides [26, 27]. STAT3-HIES patients have low Th17 cell counts, whereas DOCK8-HIES patients are suspected of having malfunctioning Th17 cells [9]. This failure of innate immunity in epithelial cells likely is the cause of increased susceptibility to bacterial and fungal infections of the skin and airways [9, 28]. Furthermore, HIES patients have a lack of high-affinity antigen-specific antibodies [29, 30]. In STAT3-HIES patients, this might be caused by reduced somatic hypermutation for several antibody types leading to impaired affinity maturation, but reports remain conflicting [29]. DOCK-HIES patients likely have a defective T-cell and B-cell interaction, again leading to impaired affinity maturation [31, 32]. The lack of high-affinity antigen-specific antibodies means that HIES patients have an impaired adaptive immune response, further explaining the recurrency and severity of infections.

DOCK8-HIES patients have also been shown to be more vulnerable to viral infections of the skin; however, this is uncommon in STAT3-HIES [30]. DOCK8-HIES patients are thought to have defects in both the innate and adaptive immune response to viruses. Firstly, natural killer (NK) cells with suppressed DOCK8 show defective cytotoxicity [33]. Secondly, DOCK8 deficient NK and T cells have a predisposition to undergo cell death when migrating through tissue, likely limiting the number of cytotoxic cells that could reach virally infected skin [34]. Overall, the defective response of NK and T cells likely allows for poor control of viral pathogens in patients with DOCK8-HIES [30]. Overall, both AD and HIES patients have an increased susceptibility to infections; however, due to the differences in underlying physiopathology, the type of infection, as well as the predominance of certain pathogens, differ. Infectious complications in patients with AD are usually limited to the skin and can be caused by bacteria, viruses, and fungi [2]. In rare cases, usually in severe AD, a skin infection can lead to systemic complications and hospitalisations [13]. A common cause of systemic complications is EH, which can include encephalitis and septic shock [35]. Furthermore, systemic complications from bacterial infections can include osteomyelitis and septic arthritis [13]. In HIES patients, infectious complications of the skin are also common [9, 10]. In STAT3-HIES patients, skin infections are usually caused by bacteria or fungi, while in DOCK8-HIES patients, viral skin infections are often found [9-11]. Importantly, and in contrast with AD patients, the spectrum of infections seen in HIES patients is not limited to the skin [30, 36]. While, like in AD, HIES patients are susceptible to skin infections with *S. aureus*, HIES patients are also susceptible to invasive *S. aureus* infections. Patients with HIES often experience infections of the airways, including upper respiratory infections, pneumonia, and bronchitis [30, 36]. Furthermore, infectious complications such as osteomyelitis, internal abscesses, and sepsis are common [10, 30]. Thus, infection susceptibility in AD is linked to the damaged skin barrier, and skin infections are expected, while in HIES infection susceptibility is linked to a dysfunctional immune system and infections of both the skin and invasive infections, such as those affecting the airways or bones, are expected.

Diagnosis

Multiple diagnostic criteria for AD are in use but involve a combination of the main feature of itchy skin with some minor features, including a history of dry skin and a personal or family history of allergies [37]. AD predisposes patients to skin infections and likely also to some extracutaneous infections, such as ear infections and urinary tract infections, although the mechanism behind this remains unclear [38, 39]. Furthermore, AD is strongly associated with the development of allergies, such as allergic rhinitis, asthma, and food allergies [40]. Thus, the clinical presentation of AD includes not only dermatitis but also infections and allergies. HIES patients have a strong overlap in presentation with AD patients. Dermatitis, high serum IgE levels, and a predisposition to skin infections are all seen in both HIES and AD patients [9, 11, 13]. Furthermore, DOCK8-HIES patients often present with allergies, but allergies are also strongly associated with AD [11, 30, 40]. This strong overlap begs the question of when to suspect HIES and refer the patient to a specialist.

There are several findings that should raise the suspicion of HIES in a patient presenting with AD. In the case of STAT3-HIES, these are often skeletal, dental, and connective tissue abnormalities [10]. These clinical features present as bone fractures without apparent trauma, pathological rendition of primary teeth, scoliosis, hyperextensible joints, and characteristic facial features [7, 9, 10]. HIES patients are also at increased risk for benign tumours and malignancy [9, 30]. Family history can also help identify HIES. Strong indicators are a family history of HIES, unexplained family member death, and, especially in DOCK8-HIES, consanguinity [9, 10, 30]. Overall, these findings help distinguish HIES from AD. However, young children might not yet display skeletal, dental, and connective tissue findings or malignancy [9]. Therefore, to identify HIES in young children, it is crucial to consider infections as an indicator of HIES.

In patients with HIES, infections are known to be severe, recurrent, and sometimes even life-threatening due to their impaired immune system [7, 30]. Serious infectious complications such as internal

abscesses and sepsis are common, and, considering the recurrent feature of HIES, patients experience multiple infections per year, often lasting for multiple weeks [10, 41]. As AD patients are susceptible to skin infections, skin infections should only be considered an indicator of HIES if associated with infectious complications or if they are recurrent [9]. DOCK8-HIES patients are particularly vulnerable to viral skin infections, and, in contrast to AD, which is mainly associated with EH caused by *HSV-1*, DOCK8-HIES patients often experience infections with a wide variety of viruses, including *varicella-zoster, molluscum contagiosum*, and *human papillomaviruses* [11, 30, 43]. Thus, recurrent viral infections by multiple viruses are an indicator of DOCK8-HIES [30]. Furthermore, the HIES susceptibility to severe and recurrent airway infections is not found in AD [38]. Thus, the occurrence of multiple pulmonary infections per year that need treatment with antibiotics is a good indicator of HIES [9-11]. In turn, these recurrent pulmonary infections in HIES patients can lead to the development of bronchiectasis [10, 43].

Overall, while AD patients are also at increased risk of skin infections, infections that should raise suspicion of HIES include recurrent and severe bacterial and fungal skin infections, recurrent invasive infections, and, in the case of DOCK8-HIES, recurrent and severe viral skin infections. When children with AD-like eczema present with these HIES infection patterns, a follow-up should take place where the child is evaluated for other signs of HIES [9]. The National Institutes of Health HIES scoring guideline followed by genetic testing can be used to confirm a HIES diagnosis [7]. Thus, symptoms of AD and HIES can overlap, but important indicators for HIES include recurrent and invasive infections, skeletal, dental and soft tissue abnormalities, malignancy, and family history (figure 1).

Treatment

Treatment of AD is focused on maintaining skin barrier function. As transepidermal water loss is an essential aspect of skin barrier dysfunction, patients with AD are recommended to hydrate and moisturise their skin daily [4]. When regular hydration and moisturisation fails to improve dermatitis, topical anti-inflammatory medications, such as topical corticosteroids, can improve skin barrier functions [4]. Usually, bacterial infections and fungal infections are easily treated with oral antibiotics and topical anti-fungal creams, respectively [2, 25]. Suspicion of eczema herpecticum should be quickly treated with systemic anti-viral medication to prevent serious complications [35]. In cases of severe AD, where previously mentioned treatment has failed to control severe dermatitis, phototherapy or systemic immunosuppressants can be considered [4].

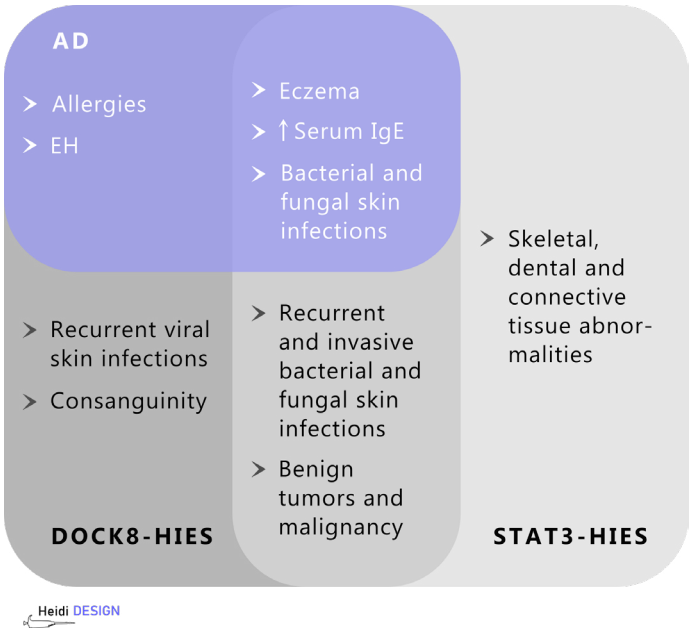

***Figure 1**: Symptoms and complications of atopic dermatitis (AD), STAT3-HIES, and DOCK8-HIES. HIES = Hyper-IgE syndromes, EH = eczema herpeticum.*

Management of HIES focuses on the prevention and treating of infections. Prophylaxis treatment with anti-bacterial, anti-viral, and anti-fungal medication can help prevent these infections [9, 30]. Additionally, an HSCT treatment can be recommended as high morbidity and mortality are associated with the condition [30]. However, HSCTs necessitate the availability of a suitable donor and are not without risks, meaning this treatment is not always a viable option and must be carefully considered [30]. Initial reports of HSCT in STAT3-HIES patients were doubtful about its effectiveness as no reduction of IgE levels took place [44]. However, a recent long-term follow up found that HSCT in all eight STAT3-HIES patients greatly reduced infections and even completely abolished skin infections [45]. The effectiveness of HSCT in DOCK8-HIES patients has been reported in many case reports and, recently, in a larger retrospective study of 71 patients by Aydin *et al.* [44-46]. Patients were found to have improved or abolished eczema (99%) and greatly reduced or abolished pulmonary infections (93%) [46].

Diagnosing HIES at a young age is incredibly important, as it not only allows prophylaxis initiation and quick treatment of infections to help prevent long-lasting damage but also allows for the consideration of treatment with an HSCT at a young age. Performing HSCT at a young age means that the patient is less likely to have already developed long-lasting damage from previous infections or to have developed malignancy [41]. Furthermore, a case report of HSCT in two siblings with DOCK8-HIES found that the patient who received an HSCT at eight months old had more improved symptoms than the patients who received an HSCT at eight years old, indicating that perhaps transplantation at a young age is beneficial for HIES patients [9]. However, an ideal age range for HSCT in DOCK8-HIES patients could not be determined by Aydin *et al.* and likely requires analysis of much larger patient groups [46].

Conclusion

All in all, while AD and HIES have significant overlap in their clinical presentation, there are several observations that should raise suspicion of HIES. At a young age, primarily frequent and severe infections of the skin and airways set apart the more strongly immunological compromised HIES patient from the AD patient. Early diagnosis of HIES is crucial as it allows for screening for infection, initiation of prophylaxis, and consideration of HSCT, which can greatly reduce the morbidity and mortality associated with these conditions.

Acknowledgements

RAMS would like to thank Stefanie Henriet, MD-PhD, specialist in Pediatric Infectious Diseases and Immunology, and Arno Stellingwerf, BSc, for providing the author with feedback.

References

1. Mortz, C.G., *et al.* It looks like childhood eczema but is it? *Clinical and Experimental Allergy* **49**, 744-753 (2019).
2. Brar, K.K., et al. Strategies for Successful Management of Severe Atopic Dermatitis. *The Journal of Allergy and Clinical Immunology: In Practice* **7**, 1-16 (2019)
3. Verboom, P., *et al.* The cost of atopic dermatitis in the Netherlands: An international comparison. *British Journal of Dermatology* **147**, 716-724 (2002).
4. Boguniewicz, M., *et al.* Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. *Annals of Allergy, Asthma and Immunology* **120**, 10-22.e12 (2018).

5. Picard, C., *et al.* International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. *J Clin Immunol* **38**, 96-128 (2018).
6. Jonkman-Berk, B.M., *et al.* Primary immunodeficiencies in the Netherlands: National patient data demonstrate the increased risk of malignancy. *Clinical Immunology* **156**, 154-162 (2015).
7. Al-Shaikhly, T. & Ochs, H.D. Hyper IgE syndromes: clinical and molecular characteristics. *Immunology and Cell Biology* **97**, 368-379 (2019).
8. Hagl, B., *et al.* Somatic alterations compromised molecular diagnosis of DOCK8 hyper-IgE syndrome caused by a novel intronic splice site mutation. *Scientific Reports* **8**, 1-10 (2018).
9. Hagl, B., *et al.* Key findings to expedite the diagnosis of hyper-IgE syndromes in infants and young children. *Pediatric Allergy and Immunology* **27**, 177-184 (2016).
10. Schimke, L.F., *et al.* Diagnostic approach to the hyper-IgE syndromes: Immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *Journal of Allergy and Clinical Immunology* **126**, 611-617.e611 (2010).
11. Kasap, N., *et al.* A set of clinical and laboratory markers differentiates hyper-IgE syndrome from severe atopic dermatitis. *Clinical Immunology* **223**, 108645-108645 (2021).
12. Narla, S. & Silverberg, J.I. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Annals of Allergy, Asthma and Immunology* **120**, 66-72. e11 (2018).
13. Wang, V., *et al.* The infectious complications of atopic dermatitis. *Annals of Allergy, Asthma and Immunology* **126**, 3-12 (2021).
14. Kuo, I.H., *et al.* The cutaneous innate immune response in patients with atopic dermatitis. *J Allergy Clin Immunol* **131**, 266-278 (2013).
15. Cabanillas, B. & Novak, N. Atopic dermatitis and filaggrin. *Curr Opin Immunol* **42**, 1-8 (2016).
16. Kantor, R. & Silverberg, J.I. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Review of Clinical Immunology* **13**, 15-26 (2017).
17. Elias, P.M. & Steinhoff, M. "Outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol* **128**, 1067-1070 (2008).
18. Kopfnagel, V., *et al.* Expression of antimicrobial peptides in atopic dermatitis and possible immunoregulatory functions. *Curr Opin Allergy Clin Immunol* **13**, 531-536 (2013).
19. Ong, P.Y., *et al.* Endogenous Antimicrobial Peptides and Skin Infections in Atopic Dermatitis. *New England Journal of Medicine* **347**, 1151-1160 (2002).
20. Berdyshev, E., *et al.* Lipid abnormalities in atopic skin are driven by type 2 cytokines. *JCI insight* **3**, 1-15 (2018).
21. Totté, J.E.E., *et al.* Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. *British Journal of Dermatology* **175**, 687-695 (2016).
22. Kim, J., *et al.* Interactions between atopic dermatitis and staphylococcus aureus infection: Clinical implications. *Allergy, Asthma and Immunology Research* **11**, 593-603 (2019).
23. Boguniewicz, M. & Leung, D.Y.M. Recent insights into atopic dermatitis and implications for management of infectious complications. *Journal of Allergy and Clinical Immunology* **125**, 4-13 (2010).
24. Leung, D.Y.M. Why is eczema herpeticum unexpectedly rare? *Antiviral Research* **98**, 153-157 (2013).
25. Thammahong, A., *et al.* The clinical significance of fungi in atopic dermatitis. *International Journal of Dermatology* **59**, 926-935 (2020).
26. Liang, S.C., *et al.* Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *Journal of Experimental Medicine* **203**, 2271-2279 (2006).
27. Zheng, Y., *et al.* Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. *Nature Medicine* **14**, 282-289 (2008).
28. Kane, A., *et al.* STAT3 is a central regulator of lymphocyte differentiation and function. *Current Opinion in Immunology* **28**, 49-57 (2014).
29. Van De Veen, W., *et al.* Impaired memory B-cell development and antibody maturation with a skewing toward IgE in patients with STAT3 hyper-IgE syndrome. *Allergy: European Journal of Allergy and Clinical Immunology* **74**, 2394-2405 (2019).
30. Biggs, C.M., *et al.* DOCK8 deficiency: Insights into pathophysiology, clinical features and management. *Clinical Immunology* **181**, 75-82 (2017).
31. Randall, K.L., *et al.* Dock8 mutations cripple B cell immunological synapses, germinal centers and long-lived antibody production. *Nature Immunology* **10**, 1283-1291 (2009).
32. Jabara, H.H., *et al.* DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. *Nature Immunology* **13**, 612-620 (2012).
33. Ham, H., *et al.* Dedicator of Cytokinesis 8 Interacts with Talin and Wiskott-Aldrich Syndrome Protein To Regulate NK Cell Cytotoxicity. *The Journal of Immunology* **190**, 3661-3669 (2013).
34. Zhang, Q., *et al.* DOCK8 regulates lymphocyte shape integrity for skin antiviral immunity. *Journal of Experimental Medicine* **211**, 2549-2566 (2014).
35. Seegraber, M., *et al.* Recurrent eczema herpeticum - a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients. *J Eur Acad Dermatol Venereol* **34**, 1074-1079 (2020).
36. Mogensen, T.H. STAT3 and the Hyper-IgE syndrome. *Jak-Stat* **2**, e23435-e23435 (2013).
37. Ponsford, M.J., *et al.* Hyper-IgE in the allergy clinic––when is it primary immunodeficiency? *Allergy: European Journal of Allergy and Clinical Immunology* **73**, 2122-2136 (2018).
38. Serrano, L., *et al.* Association between atopic dermatitis and extracutaneous bacterial and mycobacterial infections: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology* **80**, 904-912 (2019).
39. Ren, Z. & Silverberg, J.I. Association of Atopic Dermatitis with Bacterial, Fungal, Viral, and Sexually Transmitted Skin Infections. *Dermatitis* **31**, 157-164 (2020).
40. Zheng, T., *et al.* The atopic march: Progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy, Asthma and Immunology Research* **3**, 67-73 (2011).
41. Aydin, S.E., *et al.* DOCK8 Deficiency: Clinical and Immunological Phenotype and Treatment Options - a Review of 136 Patients. *Journal of Clinical Immunology* **35**, 189-198 (2015).
42. Gennery, A.R., *et al.* Bone marrow transplantation does not correct the hyper IgE syndrome. *Bone Marrow Transplantation* **25**, 1303-1305 (2000).
43. Harrison, S.C., *et al.* Hematopoietic Stem Cell Transplantation Resolves the Immune Deficit Associated with STAT3-Dominant-Negative Hyper-IgE Syndrome. *Journal of Clinical Immunology* (2021).
44. Barlogis, V., *et al.* Successful allogeneic hematopoietic stem cell transplantation for DOCK8 deficiency. *Journal of Allergy and Clinical Immunology* **128**, 420-422.e422 (2011).
45. Ghosh, S., *et al.* Haploidentical stem cell transplantation in DOCK8 deficiency - Successful control of pre-existing severe viremia with a TCRaß/CD19-depleted graft and antiviral treatment. *Clinical Immunology* **152**, 111-114 (2014).
46. Aydin, S.E., *et al.* Hematopoietic Stem Cell Transplantation as Treatment for Patients with DOCK8 Deficiency. *The Journal of Allergy and Clinical Immunology: In Practice* **7**, 848-855 (2019).